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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/662,649	09/14/00	JAYYOSI Z	02481.1690

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EXAMINER
PATEL, S

ART UNIT	PAPER NUMBER
1624	8

DATE MAILED: 08/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/662,649	Yayyosi et al.
Examiner	**Art Unit**
Sudhaker Patel	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 29, 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-37, 47, 48, 53-59, 61-66, 70, and 91-96* is/are pending in the applica

4a) Of the above, claim(s) *3-7, 9-14, 16-25, 32-37, 70, and 93-95* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 8, 15, 26-31, 47, 48, 53-59, 61-66, 91, 92, and 96* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Applicants' communication paper # 7 dated 6/29/01 is acknowledged.

As already acknowledged in the earlier Office Correspondence, it is noted that this application is continuation of international application No.PCT/US00/11833, filed on April;, 28, 2000.

This application has been found to lack unity of invention. Applicants traverse restriction/election on the grounds that not enough support by way of providing reasons has been cited, and also the current examination would not be unduly burdensome or prolonged for the examination of instant application as a single invention, and therefore the restriction requirement is inappropriate, and is contrary to the rules.

This is not found persuasive because the claims lack unity of invention. The claims lack unity of invention because compounds of generic Formula of claim 1 do not possess single structural element that is shared by all of the alternatives that is inventive. The Formulae arrived at by computing values of Ar I, Ar II, Z, A,B, E,Z, R1-R8, with integers a,b,c,d,g,h,etc. where applicable do not share a common structural feature(s) , and the only common properties shared by all the compounds is presence of multiples of possibilities by computing the values of ArI,ArII, A, B etc. In its simplest meaning (= Heterocycle-alkyl-0- phenyl--0-alkyl)when all integers are = zero we arrive at a common sore: ArI-A-ArII-B-E-Z where in both ArI and ArII are presented as aryl, fused aryl, fused arylheterocycle, heteroaryl etc. as claimed herein which does not represent

patentable advances over the prior art already known(see WO 8705510 dated 9/1987 also cited as CAPLUS 1988:422970; USP 4567184 also cited as CAPLUS 1989:534011).

The special technical feature is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art(s).

The feature is, thus, not special if it is known. That what is common here is: Heterocycle-alkyl-0- phenyl--0-alkyl core or in its simplest chemical form a fused/unfused cyclic ring having 6-membered phenyl aryl/cyclic ring having bridge(s) as -CH2-0- or -0-CH2- which constituted the key molecule of the invention. The claims are drawn to making of structurally dissimilar derivatives or compounds which are classified separately, require separate literature searches and are not art recognized equivalents. They are made and used separately e.g. variation in values of Ar I, Ar II, Z, A,B, E,Z, R1-R8 where applicable alone in chain/ring nature & size of the heterocycle(s) with/without substituents together with the various chain length (s) for integers a,b,c,d,g,h varying from 0 to 6 where applicable . as groups would provide multiples of compounds.

Note that compounds, corresponding compositions, a method of use and the first recited process of making composition that are of the same scope are considered to form a single inventive concept under PCT Rule 13.1, 37 CFR 1.475(d). The species as presented by various groups and either compounds or their derivatives as recited by generic Formulae are not so linked as to form a single inventive concept. The compounds are so diverse in scope that a prior art of making it or its composition and using the same further as an therapeutical which is

anticipated under 35 U.S.C. 102 would not render obvious another compound of the same claim 35 U.S.C. 103.

The variation(s) in variation in values of Ar I, Ar II, Z, A,B, E,Z, R1-R8 where applicable together with presence of A/B = O,S,N,CO,-NRCO- or -CO-NR- etc. group(s) produce patentably distinct compounds that will support separate patents. It is too burdensome, in the limited time provided, to examine the entire extent of claim 1. The structural Formulae as presented by the applicants, namely, Formula (I),and its variations with claimed different values for ArI and ArII are not representing a single compound, but multiples of chemically different molecules which are not identical, and they individually/independently include various combination(s) of hydrocarbons including aliphatic and aromatic embracing heterocycles with any number of heteroatoms, and any size of the ring(s) which is too indefinite to classify. The variations of various groups as outlined above produce different entity that is presently multiple search areas.

Although it is true that electronic searching tools are available, each group must be searched separately as each represent multiples of compounds, and therefore many references by way of hits.

It is regretful that applicants will have to file divisional applications for desired protection. However, without restriction/election, an effective and complete search cannot be accomplished in the limited time available for a through examination of the entire content(s) of the invention(s). Applicants are also reminded that usually a patent protection is sought for a single invention only.

This application has been found to contain more than one invention. Therefore, restriction to one of the distinct inventions is required.

The Examiner finds Applicants' arguments are not persuasive concerning traversal of the restriction; therefore, the finding is Maintained and made ***FINAL***. Applicant is required to confirm their election, and also to cancel the non elected subject matter in the next communication.

Furthermore, according to 37 CFR 1.499(see MPEP 1893.03(d)), the examiner may in office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted, if the Examiner finds that a national stage application lacks unity of invention under CFR 1.475.

Applicants' election of the subject matter with traverse of Group XII, claims(in part) 1-2,8,15,26-31,47-48,53-59,61-66,91-92,96, drawn to compounds, corresponding compositions, a method of use of generic Formula (I) wherein Ar I (Heterocycle optionally substituted);Ar II (= phenyl, optionally substituted); A (= -0(C(R15)(R16))g-0-;B/E(= a chemical bond); Z (= non-heterocycle);c/d(= zero);R1-R4 (= independently H, Halogen or alkyl; and the species of the compound of Example 51 cited on page 95 lines 12-17 of the specification(= 2-methyl-6-(3-(2-phenyl-oxazol-4-ylmethoxy)-propoxymethyl)-benzoic acid).Since claims 1-2,8,15,26-31,47-48,53-59,61-66,91-92,96, link with other inventions they would be examined bearing in mind the subject matter as elected by the applicants only. Applicants are urged to cancel the non-elected

claims and also limit the scope of the claims to the subject matter as elected in reply to this Office Action. Claims 3-7,9-14,16-25,32-46,49-52,60,67-90,93,94,96 would not be considered as they constitute non-elected invention, 37 CFR 1.142(b).

Specification

1. The abstract of the disclosure is objected to because it consists of lengthy pages. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 U.S.C. § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2,8,15,26-31,47-48,53-59,61-66,91-92,96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim subject matter which applicant regards as the invention.

A). Claim 1 recites Ar I, Ar II as: "aryl, fused aryl, fused arylheterocycle, heteroaryl etc." This is indefinite because we are not exactly and specifically told about the nature, size of the rings, and nature, number of heteroatoms(where applicable, and the exact point of attachment to the main core. The reader is lost in visualizing the possibilities.

B). The claim language recited"optionally substituted". This is indefinite because we are not told exactly and specifically about the number, and point of attachment and carbon number.

C). On page 128 claim 25 is missing. Applicants' intentions are not known.

D). In claims 27,28 the term: "radicals" is recited which is indefinite because a radical is usually a group having unshared electron.

E). Applicants' preliminary amendments paper # 5 dated 9/14/00 does not affirm the basis for the same. Above all, there is not any specific mention of deletion or addition and its correlation either with the canceled claims or specification. Note, amendment for claim 33, page 30, line 19 could not be made as it does not exist.

F). Claims 91,92 define ring system : " ring system substituent is selected from the group..... consisting..... (un)substituted-thienyl, (un)substituted-phenyl".

This is indefinite because we are exactly and specifically not told about the point of attachment and the carbon atom involved.

G). Claim 55 recites as: " disease associated with.....free fatty acids(FFA), or triglycerides". This is indefinite because applicants remain silent about exact and specific nature of FFA as well as triglycerides.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2,8,15,26-31,47-48,53-59,61-66,91-92,96 are rejected under 35 U.S.C. 112, para one, as containing subject matter which was not described in the specification in such a way

as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are are rejected under 35 U.S.C. 112, para one because the specification, while enabling as a compound for a method for treatment of a physiological disorder which is Type II diabetes , does not reasonably provide enablement for method for the **treatment for a patient** suffering from a physiological disorder(s) or disease(s) consisting of cardiovascular condition, hyperlipidemia, hypertension, and other conditions, both by the **single** compound, and its pharmaceutical composition comprising pharmaceutically acceptable amount of the compound according to claim 1 and a pharmaceutically acceptable carrier. Most of the compounds have ArI=(Heterocycle)-0-(C(R15/R16)g-0--phenyl--Non-heterocycle core common whereas the claim language include many substituted compounds as represented by variables outlined in above mentioned claims.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPO 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPO 546. The factors include:*(1).* The nature of invention;*(2).* the state of prior art ;*(3).* the predictability or lack thereof in the art;*(4).* the amount of direction or guidance present;*(5).* the presence or absence of working examples;*(6).* the breadth of the claims, and *(7).* the quantity of experimentation needed.

The claims are drawn to compounds, pharmaceutical compositions, generic method(s)(but not limited to)for compound(s) capable of having PPAR ligand binding activity) in

a patient comprising administering to said patient a pharmaceutically effective amount of a compound or a pharmaceutically acceptable salt thereof. Thus, claims remain silent about specific use method.

1). The nature of the invention: The compounds and method of use claim(s) are drawn in part for a compound or its pharmaceutical composition which is capable of treating physiological disorder associated with PPAR ligand activity.

2). The state of prior art: There are no known compounds of similar structure which have been demonstrated to treat other conditions as claimed herein, characterized in that a compound of claim(s)1 or its pharmaceutical composition comprising administering to said patient a pharmaceutically effective amount of a compound or a pharmaceutically acceptable salt thereof according to the claims under consideration, is used.

3). The predictability or lack thereof in the art: It is presumed in the treatment of the physiological disorder(s) as claimed herein there is a way of identifying those patient(s) who may develop any kind of suffering from physiological disorder(s) related to PPAR ligand binding activity as recited. There is no evidence of record which would enable the skilled artisan in the identification of the patient(s) who have the potential of becoming afflicted with the condition(s) related to PPAR ligand binding activity as claimed herein.

4). The amount of direction or guidance present and **5).** The presence or absence of working examples: There are no doses present to direct one to protect a potential patient from the physiological disorder(s)cited, etc. There are no doses present for treatment of the disorder of the

cardiovascular condition , and other physiological disorder related to hyperlipidemia, hypertension and condition(s) cited, etc. , and there is no data present for the reduction or increase of the physiological disorder related to PPAR ligand binding activity in a patient which may include humans

.6). The breadth of the claims: The claims are drawn to generic treatment of diseases(s)/condition(s) that is related to physiological disorder(s) related to PPAR ligand binding activity in a patient suffering from condition or disease related to said activity.

7). The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

In view of the extreme difficulties that have been and are still being encountered in the treatment of diseases related to physiological disorder related to cardiovascular condition, and other conditions as recited herein such utilities are unbelievable on their face and therefore they must be supported by sufficient evidence demonstrating such utilities. All available drugs for treatment of disease related to physiological disorder, namely cardiovascular condition, hypertension, hyperlipidemia etc. could be used in a limited way, and provide protection mostly by inducing undesirable side effects.

Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a single compound for a method of treating diabetes Type II as well as other diseases, conditions etc. simultaneously. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has been accomplished, *In re Ferens*, 163 USPO 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPO 2nd 1001, 1006.

Claim Rejections - 35 U.S.C. § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2,8,15,26-31,47-48,53-59,61-66,91-92,96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Youssefyeh et al.(WO8705510 dated 9/24/1987also cited as CAPLUS 1988:422970), and also over Musser et al.(USP 4794188 dated 12/27/1988, and also cited as CAPLUS 1989:534011).

The instant application is related to making of Di- aryl acid substituted derivatives which are represented by a generic Formulae of claim 1 wherein acid is the benzoic acid.

Applicants further claim pharmaceutical composition which comprises a compound and pharmaceutically acceptable carrier as ingredients, and finally they also claim their function as a method of treating a patient suffering from a physiological disorder related to PPAR ligand binding activity.

The ref.'510 differs from the instant application by not having the groups R1- R8 with or without A,B linking groups as listed in instantly claimed compounds. See Formula I on page 147, and compound at the bottom. However, the reference does teach the common structure Phenyl fused to heterocycle-CH2-0-phenyl-CN, and also a utility of the compounds as inflammation inhibitors and allergy inhibitors.

The other ref.'188 also teaches making of heterocyclic ethers having antiinflammatory antiallergic activity. The reference differ from the instantly claimed compounds by not having specific R1-R8 with A,B bridges on to the phenyl/heterocycle ring. However the reference does teach phenyl substitution in 4-positions. See Formula I & II on page 1 and their utility as materials for pharmaceutical use.

Thus, it would have been obvious to one having ordinary skill in the art at the time of invention to prepare instant compounds by modifying the core of generic Formulae having phenyl/phenyl substituted heterocycle-Bridge-Phenyl having -C00H group i.e. substituting Salicylic acid with modification in that -C00H group is replaced as -CH2-C00H group, of any or both of the ref. and try out various derivatives by putting/ inserting extra groups for H atoms in the molecule as claimed herein, and also to try out the use/utility similar to references or

improved multipurpose use by way of substitution of A or B bridged respectively for H atoms of the references as claimed herein by using the conventional chemistry knowledge. The motivation stems from the expectation of making compounds having equal or better physiological activity or function related to PPAR ligand binding activity.

It has been held that a prior art disclosed compounds is sufficient to render a prima facie case of obviousness as species falling within a genus. See In re SUSI, 440 F 2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by Federal Circuit in Merck & co. V. Biocraft Laboratories, 847 F 2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir.1989).See In re Dillon 16 USPQ 2nd. 1897, 1923 regarding a prima facie case of obvious ness of structurally similar compounds disclosed by prior art" regardless lo the properties disclosed in the inventor's application.

This application has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is, therefore, requested in promptly correcting any errors of which they may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel,D.Sc.Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

S.p.

August 21, 2001.

Mukund J. Shah

Mukund Shah

SUPERVISORY PATENT EXAMINER

ART UNIT 1624